Comparison of tumor dynamics models and tumor growth inhibition metrics in support of decisions in early Phase Ib/II clinical oncology studies

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Background & Objective

Model-derived Tumor Growth Inhibition (TGI) -> predictors of overall survival (OS).
Limitations during early drug development:

- Short follow-up (FU)
- Small number of tumor scans

To extend the work: **TGI metrics have superior operating characteristics (OCs) than RECIST endpoints to support early decision [1]**

➔ various biexponential models relying on different hypotheses were used to estimate TGI parameters/metrics

➔ OC for TGI parameters/metrics were assessed within models and across the models

Methods

Models

Description of the TGI models used

Model	Equation	t is the time (week) with time 0 at the start of treatment; TS is the tumor size (SLD in mm), TS0 at the start of treatment (TS(0))
Stein [2]	$TS(t) = \begin{cases} TS_0 \cdot e^{KG \cdot t} & if\ t < 0 \\ TS_0 \cdot (e^{-KS \cdot t} + e^{KG \cdot t} - 1) & ,if\ t \geq 0 \end{cases}$	KS, tumor shrinkage rate constant ([week]-1) KG, tumor growth rate constant ([week]-1)
sTGI (Claret) [4,5]	$TS(t) = \begin{cases} TS_0 \cdot e^{KL \cdot t} & if\ t < 0 \\ TS_0 \cdot e^{KL \cdot t - \frac{KD}{\lambda} \cdot (1 - e^{-\lambda \cdot t})} & ,if\ t \geq 0 \end{cases}$	KL, tumor growth rate constant ([week]-1) KD, tumor growth rate constant ([week]-1), that decrease exponentially with time according to λ ([week]-1)
gStein (Generalized) [3]	$TS(t) = \begin{cases} TS_0 \cdot e^{KGR \cdot t} & if\ t < 0 \\ TS_0 \cdot \left((1 - F) \cdot e^{KGR \cdot t} + F \cdot e^{-KSS \cdot t}\right) & ,if\ t \geq 0 \end{cases}$	KGR, tumor growth rate constant ([$week$]-1), KSS, tumor shrinkage rate constant F, a fraction of the tumor was sensitive to the drug, with (1-F) being resistant, so that regression of the tumor began at (F· the initial tumor quantity) and regrowth began at fraction ((1 -F) · the initial tumor quantity)

Key differences between the TGI parameters across models
Stein: No assumption on treatment effect.
KS, KG on-treatment shrinkage and growth rates.
Pre-treatment KG unknown since only one pre-treatment scan.
Claret: Treatment effect on shrinkage (KD) that decreases with time (Lambda). KL pre-treatment growth rate . LAMBDA : resistance;
gStein: Treatment effect on sensitive cells (F, KSS) and growth due to insensitive cells (1-F, KGR)

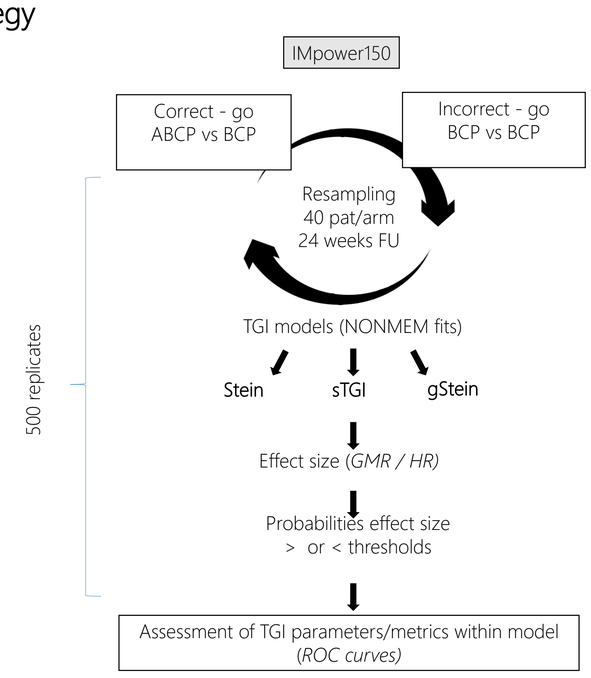
Introduction of TGI metrics
Tumor ratios are derived at 6, 12, 18 and 24 weeks, and at maximum shrinkage TRmax.
TTG was calculated as follows:

Model	Equation TTG
Stein [2]	$(Log(KS) - \log(KG))/(KS + KG)$
sTGI (Claret) [4,5]	$(Log(KL) - \log(KD))/\lambda$
gStein (Generalized) [3]	$(Log((KSS * F)/(KGR * (1 - F))/(KSS + KGR)$

Data

In the IMpower150 study, first-line non-small cell lung cancer (NSCLC) patients were randomly assigned to atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP arm), atezolizumab, carboplatin and paclitaxel (ACP arm), or BCP (control). ABCP significantly prolonged both PFS and OS compared to BCP.

Strategy



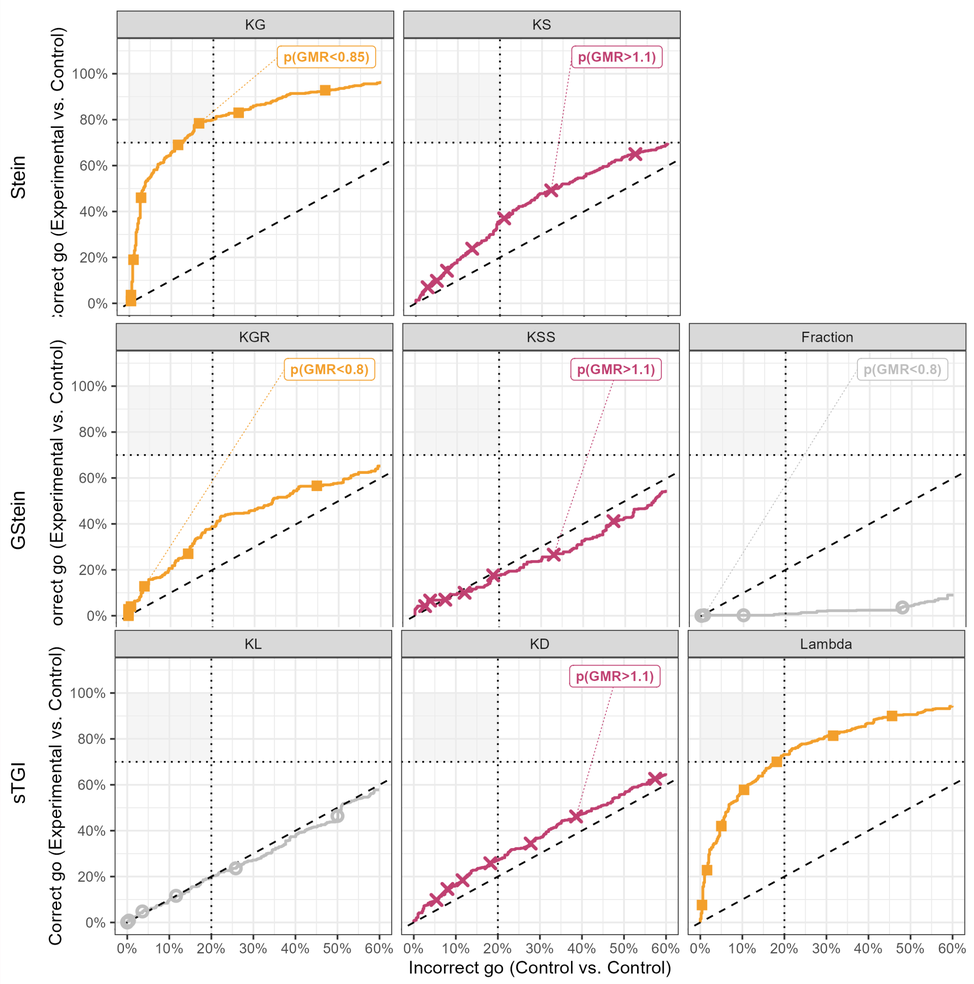
Results

Comparison of the parameters estimates of the 3 models

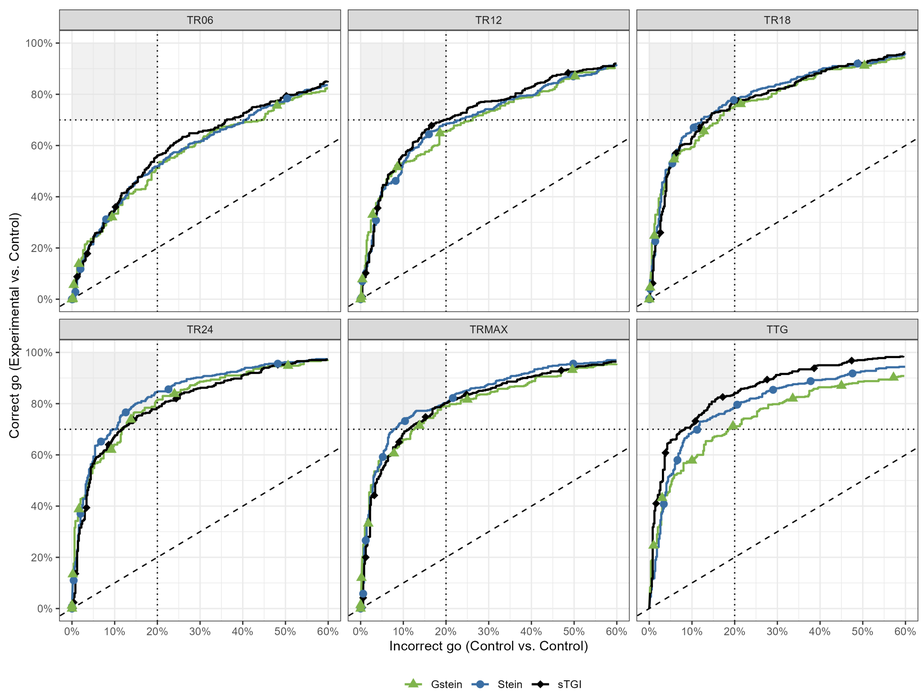
Description	Stein		sTGI		gStein	
OFV	48712.5		47085.1		47153.8	
dOFV			-1627.438		-1558.71	
	Estimate	RSE%	Estimate	RSE%	Estimate	RSE%
KG ACP	0.00888	5.9	KL	0.00452	11.2	KGR	0.00962	4.2
KG ABCP	0.0069	5.4	KD ACP	0.0689	6.2	KSS ACP	0.0783	5.8
KG BCP	0.0113	4.6	KD ABCP	0.0751	5.2	KSS ABCP	0.0856	5.3
KS ACP	0.0424	6.0	KD BCP	0.0781	7.0	KSS BCP	0.103	5.8
KS ABCP	0.0445	5.1	LAMBDA ACP	0.117	8.1	F ACP	0.391	12.3
KS BCP	0.0482	5.6	LAMBDA ABCP	0.0933	5.7	F ABCP	0.514	8.6
SLD BASELINE	65.7	2.0	LAMBDA BCP	0.159	7.7	F BCP	0.167	17.5
ERROR	37.8	7.1	SLD BASELINE	67.3	1.9	SLD BASELINE	67.4	2.1
			ERROR	26.3	7.9	ERROR	25.0	0.60
			Ω^2KL	2.1	8.8	Ω^2KGR	1.18	5.8
Ω^2KG ACP	0.682	11.5	Ω^2KD ACP	0.584	14.9	Ω^2KSS ACP	0.747	9.5
Ω^2KG ABCP	0.629	10.7	Ω^2KD ABCP	0.518	12.6	Ω^2KSS ABCP	0.698	9.7
Ω^2KG BCP	0.353	10.8	Ω^2KD BCP	0.512	11.1	Ω^2KSS BCP	0.764	10.8
Ω^2KS ACP	0.564	14.0	Ω^2LAMBDA ACP	0.966	18.3	Ω^2F ACP	1.83	15.1
Ω^2KS ABCP	0.555	11.1	Ω^2LAMBDA ABCP	0.564	13.4	Ω^2F ABCP	1.41	12.5
Ω^2KS BCP	0.560	10.5	Ω^2LAMBDA BCP	0.408	17.5	Ω^2F BCP	2.29	17.2
Ω^2BSL	0.427	4.1	Ω^2BSL	0.431	4.1	Ω^2BSL	0.427	4.9

A lognormal distribution was assumed for inter-individual variability with mean 0 and variance ω2 on each of the parameters; additive residual error.

ROC curves for model parameters



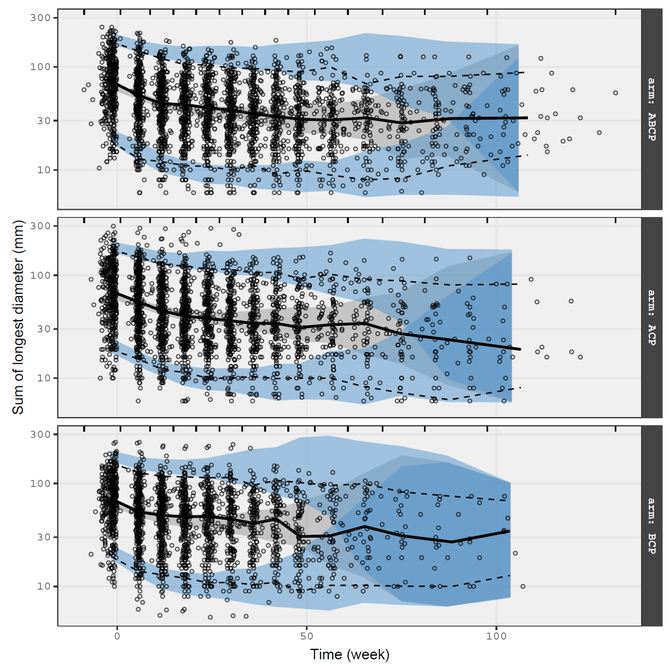
Comparison of the 3 models – 40 patients 24 w



Model estimation

- Accuracy in the estimation of the parameters for the all three models (table below)
- sTGI model outperformed both gStein and Stein models (OFV)
- All models had good model evaluation (VPC like the Stein model below).

VPC of tumor size (Stein model)



Operating characteristics on TGI parameters

- KG from Stein had good OCs with correct go rate close to 80% and incorrect go rate <20% as previously shown [1],
- Growth rate estimates with both sTGI and gStein had poor OCs with correct go rates <30%.
  - ✓ These growth rates are not impacted by the treatment.
- None of the other parameters (especially the shrinkage rates) had good OCs.

Operating characteristics

- Derived TGI metrics TR24 and TRmax had good and similar OCs (around 80% correct go rates) whatever the model used,
- TR12 and 6 were inferior.
- TTG had best correct go rate when estimated by sTGI (>80%), followed by Stein (<80%) and gStein (around 70%).

Conclusion

The sTGI best fitted complete IMpower150 study data. When applied to subsampled datasets, the only parameter with good OCs was the KG estimated using the Stein model. Derived TGI metrics (TR24, TRmax or TTG) had good performance irrespective of the model with a preference for sTGI estimated TTG.
Selecting the right TGI parameter/metric is critical for assessing treatment effects and decision-making in early oncology drug development

References

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